PSJ17 Exh 78

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FEBT Strategic Publications Plan 2005 - 2006

FEBT Publications Working Group

Updated July 2005

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Publications Program
Envision Pharma

1. Situation Analysis (Refer to section of brand plan)
2. Positioning and Messaging
3. Publications Plan Strategy
4. Tactical Publications Plan

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SWOT Analysis for FEBT Publications

Strengths	***Weaknesses***
▪ Data on product benefits* - Rapid onset of analgesia - Formulation/high lipophilicity - FEBT vs OTFC data and switching data ▪ Clinical development plan on track to provide data for publications ▪ Publications plan in place	▪ Limited KOL involvement and buy-in ▪ Diverse target audience
Opportunities	***Threats***
▪ Build awareness and sense of urgency to diagnose and treat BTP - BTP is not consistently defined worldwide - Blunt perceptions around A/A/D and opiophobia ▪ Create a new class: rapid-onset opioids (ROO) ▪ Potential indication in noncancer BTP	▪ Short time frame to launch ▪ Established SAO competitors and generic OTFC - Switch from current therapy

*Pending study results

Critical Success Factors Related to Pubs Program

1. Convert ACTIQ loyalists to FEBT
2. Continue to increase awareness and understanding of BTP and its optimal treatment
3. Build KOL support and physician awareness of FEBT as an effective treatment for BTP
4. Differentiate FEBT from ACTIQ and other BTP treatment options
5. Minimize risk for abuse, addiction, diversion

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Pubs Strategies/Tactics to Achieve Critical Success Factors

1. Disseminate key FEBT clinical and scientific information (present and publish PK and clinical trials)

2. Develop scene-setting and review articles to increase awareness and understanding of BTP and its optimal treatment and to minimize risk for abuse, addiction, diversion

3. Establish ROOs as a class and differentiate them from SAOs

4. Support the use of the new BTP assessment and management guidelines

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Positioning and Messaging

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2005 FEBT Scientific Concepts

- Message development will be broken into two key areas:

Disease Awareness	FEBT
>BTP as a component of chronic pain	>New delivery system
>Prevalence of BTP in cancer and noncancer conditions	>Fast onset of analgesia
>Diagnosis and treatment	>Efficacy in BTP in cancer and noncancer conditions
>Abuse/addiction/diversion	

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Disease Awareness: Chronic Pain

- Definition
  - Chronic pain is defined as pain lasting beyond normal healing time or lasting >3 to 6 months
  - Comprised of two components, persistent and BTP, each requiring distinct assessment & treatment
- About 50 million of the estimated 75 million Americans who live with "serious pain" suffer from chronic pain.[1]
- Diagnosis and treatment
- Burden of illness
  - Patients with chronic pain are 5X as likely as those without chronic pain to use health care services. In addition, medical complications associated with inadequately controlled acute pain can increase length of stay, re-hospitalization rates, and outpatient visits.[1]
  - Pain costs Americans an estimated $100 billion each year. Patients, families, health care organizations, and society bear this financial burden.[1]
- Pain is pain[2]
  - Pathophysiology of CA & non-CA patients the same regardless of etiology/underlying disease

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[1] American Pain Society http://www.ampainsoc.org/ce/npc/

[2] Turk D. Clin J Pain 2002: 18(2):75-6

Disease Awareness: BTP

- A transient exacerbation of pain that occurs in a patient with otherwise stable, baseline persistent pain.
  - Spontaneous (20-60%), incident (50-60%), or 'end-of-dose' failure (17-30%)
  - Mean duration of BTP episode of 15-30 minutes, and average frequency of 4-7 episodes/day
  - BTP greatly impacts patients' ability to function and their quality of life
  - Common mechanisms may underlie BTP in both cancer and noncancer conditions (ie, central sensitization, wind up, etc)
- Common in cancer patients—as many as two-thirds of patients may experience BTP and may be as high as 80% in patients with advanced disease
- BTP may be associated with disorders such as arthritis, sickle cell anemia, low back pain, headaches, neuralgia, and fibromyalgia
- Burden of illness/consequences of BTP
  - 15% decrease in productivity due to pain
  - 76.6% of productivity loss on the job (not due to absence)
  - Loss of 4.6 hours/week (mean)
  - Annual cost of pain related lost productivity and absence is approximately $61.2 billion
- BTP continues to be underrecognized and undertreated

Bennett D et al. Pharm Ther 2005;30(5):296-301 Svendsen KB et al Eur J Pain 2005; 9:195-206. Fortner B et al. J Pain. 2002;3(1):38-44. Burton A et al. Clin J Pain. 2004;20(3):195-7.

Cancer and Noncancer BTP Prevalence and Characteristics

- Portenoy BTP CA data (n=63)[1]
  - -64% of patients experience BTP
  - -Median # of BTP episodes per day = 4
  - -43% of patients reported onset of pain within 3 minutes
  - -Median duration of BTP episode = 30 minutes
  - -May be incident related (55%) or idiopathic
  - -Pathophysiology may be somatic (33%), visceral (20%), neuropathic (27%) or mixed (20%)
- Portenoy BTP Non-CA data (n=228)[2]
  - -74% of patients experience BTP
  - -Median # of BTP episodes per day = 2
  - -Median time to maximum intensity = 10 minutes
  - -Median duration of BTP episode = 60 minutes
  - -May be incident related (92%) or idiopathic
  - -Pathophysiology may be somatic (38%), visceral (4%), neuropathic (18%) or mixed (40%)

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[1] Portenoy & Hagen, Pain, 41 (1990), 273-281. [2] Portenoy, AAPM, Feb 23-27, 2005. Palm Springs, CA.

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Disease Awareness: BTP Management

- Managed with short-acting oral analgesics, usually opioids, given in addition to the maintenance analgesic regimen
  - The oral opioids most widely used (morphine, hydromorphone, and oxycodone) are not very lipophilic and are poorly absorbed which delays onset of analgesia making them largely ineffective in managing BTP
  - Fentanyl (a lipophilic opioid that is better absorbed and has a more rapid onset of action) has demonstrated efficacy in the treatment of BTP
- Because of shared mechanisms in chronic cancer and noncancer pain, treatment approaches may be extrapolated from the management of chronic cancer pain to pain from other causes
  - Many professional organizations and expert groups, including the American Pain Society, now support the judicious use of opioids for selected patients with chronic noncancer pain

Bennett D et al. Pharm Ther 2005;30(5):296-301
Bennett D et al. Pharm Ther 2005;30(6):354-361

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Disease Awareness: BTP Management

- The first BTP assessment and treatment guidelines were published in 2Q 2005[1,2]
  - Thorough assessment needed to determine pain pattern and distinguish BTP from persistent/baseline pain
  - BTP is a distinct component of chronic pain requiring an analgesic that matches its rapid onset and short duration
  - ROOs are an emerging class of opioids specifically designed to provide rapid analgesia to treat BTP
  - Short-acting opioids are not designed or indicated to treat BTP
  - Short-acting opioids do not provide rapid analgesia – their onset of analgesia is ~30 min or more

Bennett D et al. Pharm Ther 2005;30(5):296-301
Bennett D et al. Pharm Ther 2005;30(6):354-361

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Key FEBT Messages - MOA

- A novel delivery system, the dissolving effervescent buccal tablet, is formulated to improve the rate and efficiency of fentanyl absorption through the oral mucosa to provide rapid analgesia
- Effervescent reaction results from the release of carbon dioxide which may:
  - Adjust the pH of the microenvironment to allow more un-ionized fentanyl to form
  - Reduce the thickness of the mucosal layer of the cheek and gum
  - Open tight junctions between cells
  - Increase lipophilicity of cell membranes
- All contribute to the rapid absorption of fentanyl

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Key FEBT Messages

- Efficacy
  - Rapid onset of pain relief—significant in <15 minutes
  - Efficacy demonstrated in placebo-controlled clinical trials of BTP
- PK profile
  - Linear across 100-800 µg dose range
  - Simultaneous administration of four 100 µg doses is bioequivalent to administration of a single 400 µg dose
  - Earlier T_{max} compared to ACTIQ, which could translate to better clinical efficacy/earlier onset of analgesia
- Safety
  - Similar tolerability to other opioids
  - Typical opioid side effects, some of which cease or decrease in intensity with use
  - No respiratory depression observed in opioid-tolerant patients with cancer-related BTP
- Convenience/ease of use
  - Novel dissolving effervescent buccal tablet
  - Advantages over ACTIQ
    - Easier to use
    - Less chance for user error
    - Not on a stick

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Publications Plan Strategy

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Addressing the Challenges (1)

Challenges	Strategic Imperatives	Publications Tactics
Market preparation in short time frame	▪ High-profile presence at targeted key congresses ▪ Citable publication(s)	▪ Provide a critical mass of publications at launch ▪ Current program includes 19 abstracts, 10 1º pubs, and 5 2º pubs
Awareness of BTP diagnosis and treatment among treating MDs	▪ Educate current prescribers on diagnosis and treatment ▪ Communicate current unmet medical need	▪ Maintain focus on unmet need (efficacy/safety profile and convenience) through 2º pubs ▪ Support/educate through 1º and 2º pubs with messages on proper diagnosis and treatment: "Pain control is an important issue and how you get there matters"
Second agent approved for BTP	▪ Differentiate FEBT and position as agent of choice for BTP ▪ Prepare and build upon expanded indication	▪ 2º pubs highlighting current treatments as less than ideal - Lack of BTP trials for these drugs ▪ 1º pubs emphasizing FEBT efficacy, safety/tolerability, and QoL

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Addressing the Challenges (2)

Challenges	Strategic Imperatives	Publications Tactics
Established competitors and transition from current therapy	▪ Identify and support advocates to drive acceptance of FEBT ▪ Leverage novel MOA, rapid onset of action, cost, and convenience ▪ Define ROOs as a class separate from SAOs	▪ Work with advocates on abstracts, 1º and 2º pubs ▪ Monitor competitor activities
KOL involvement and buy-in	▪ Build and strengthen relationships with KOLs	▪ Partner with KOLs on abstracts, 1º and 2º pubs, symposia presentations, and roundtables
Opiophobia and A/A/D	▪ Emphasize safety of FEBT ▪ Blunt perceptions around A/A/D and opiophobia ▪ Tie addiction to patient behavior as well as particular drugs	▪ Once data is available, use 2º pubs to discuss issues with A/A/D potential, patient and physician concerns ▪ 1º pubs emphasizing safety

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Target Audiences

PRIMARY
Pain Medicine
Anesthesiology
Physical Medicine
Rehabilitation
Oncologists

SECONDARY
Primary Care Physicians
Palliative Care
Psychiatrists
Neurologists

TERTIARY
Pharmacists
Payers
Nurses

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Clinical Study Program: Priority Studies

- Key Studies
  - 099-14
  - 3039
  - 3042
- Prioritized studies
  - Level 1: 099-14*, 3039, 3041, 3042
  - Level 2: 1026*, 1027*, 1028*, 1029*, 3040
  - Level 3: 099-11*, 099-18*
  - Level 4 (low): 099-15, 099-16
    (lowest priority): 099-19, 099-20, 099-21

*Publications in development

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The Tactical Publications Plan

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FEBT Publications Program Objectives

- Support the overarching FEBT brand strategy through primary, secondary and review publications over the lifecycle of FEBT
  - Provide credible product positioning support with consistent language across publications concerning pain definitions, BTP prevalence and characteristics, diagnosis and treatment
  - Support key messages and product differentiation through PK/PD, clinical outcomes, and scene setting articles (eg, disease awareness)
  - Build Cephalon's reputation as a leader in the pain field through quality publications and poster/presentation presence at key scientific meetings

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FEBT Publications Program Objectives

- Set long-term, milestone driven, data dissemination strategy
  - Provide a critical mass of publications at launch 3Q 2006
  - Provide publications supporting the expanded indication for 3Q 2007
- Identify and capitalize on market opportunities
  - Raise awareness and support the use of the new BTP guidelines by referencing in all appropriate publications
  - Support the establishment of rapid-onset opioids as a new class
- Generate third-party supporters—key opinion leaders (KOLs) through involvement in the publications program

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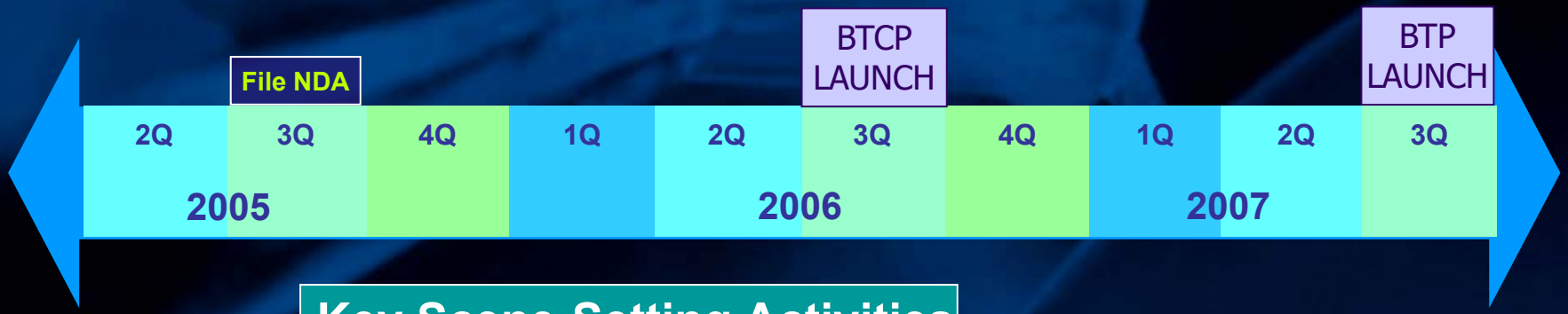
Types of Publications Activities



Key Scene-Setting Activities

Key PK Data Activities

Key Clinical Data Activities

Key Data Review Activities

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Proposed Tactics

- Congress abstracts 2005-2006
  - 17 congress abstracts/posters/presentations
    - 1 poster presentation in 2005
    - 18 submissions in 2005/06 for potential 2006 presentations
    - 11 submissions in 2006 for potential 2007 presentations
    - Other submissions possible depending on data mining
- Manuscripts 2005-2006
  - 12 primary articles to be started in 2005
    - Papers in progress: 1011, 1018, 1026, 1027, 1028, 1029, 3014
    - Others possible depending on data mining
    - Anticipated publication dates 4Q 05 through 4Q 06
  - Scene-setting/review articles to be started in 3Q 05

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Abstract Submitted to Date in 2005

Congress	Studies	Abstract Status	Location	Meeting Date
ASCO	▪ 099-14 Efficacy (shell abstract submitted as late-breaker [LB])	Rejected	Orlando	May 2005
ASA	▪ 099-11 PK ▪ 099-18 Dose-proportionality ▪ 099-19 PK (Taiho)	Accepted Rejected Rejected	New Orleans	Oct 2005

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Abstract Presentation Opportunities 2006

Congress	Potential Studies	Abstract Deadline	Location	Meeting Date
AAPMed	▪ 099-14 (efficacy) ▪ 1027 Dose Proportionality ▪ 1029 MD PK	Oct 05	San Diego	Feb 2006
APS	▪ 1028 Absol. Bioavailability ▪ 099-20 MD PK (Taiho) ▪ 099-14 (efficacy+resp. analysis, patient global ass'mt) ▪ 3039 (efficacy)	4 Nov 05	San Antonio	May 2006
SAMBA	▪ Dose Proportionality (099-11, 099-18, 1027)	Feb 06	Washington, DC	May 2006
ONS	▪ 099-14 (efficacy+resp. analysis, patient global ass'mt) ▪ 3039 (ACTIQ switch/pref+efficacy)	3 Jan 06	New Orleans	May 2006
ASCO	▪ 3039 (ACTIQ switch/pref+efficacy) ▪ 099-16 Mucositis ▪ 1026 Bioequivalence	20 Dec 05	Atlanta	June 2006

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Abstract Opportunities 2006-2007

Congress	Potential Studies	Abstract Deadline	Location	Meeting Date
ASA	▪ 3041 NeP (efficacy) ▪ 3042 LBP	1 Apr 06	Chicago	Oct 2006
AAPM&R	▪ 1027 Dose Proportionality ▪ 1028 Absol. Bioavailability ▪ 3041 NeP (ACTIQ switch/pref+efficacy)	Feb 06	Honolulu	Nov 2006
AAPMed	▪ 3041 NeP (efficacy) ▪ 3042 LBP ▪ ISS ▪ ISE	Oct 06	New Orleans	Feb 2007
APS	▪ 3040 OL Safety(x2: Safety/efficacy & Quality of life) ▪ ISS (modified AAPMed) ▪ ISE (modified AAPMed) ▪ 099-21 MD PK (Taiho)	Oct 06	Washington, DC	May 2007
ASCO	▪ 099-15 OL Safety (x2: Safety/efficacy & ACTIQ switch/pref)	Dec 06		June 2007

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Congress Presentation Dates*

ASA
- 099-11 PK

AAPMedicine
- 099-14 BTCP
- 1027 Dose Proport
- 1029 MD PK

ONS
- 099-14 BTCP
- 3039 BTCP

APS
- 1028 Abs Bioavail
- 3014 BTCP
- 3039 BTCP

SAMBA
- Dose Proport

ASCO
- 3039 BTCP
- 099-16 Mucositis
- 1026 Bioequivalence

AAPM&R
- 1027 Dose Proport
- 1028 Abs Bioavail
- 3039 BTCP
- 3041 NeP

ASA
- 3041 LBP
- 3042 NeP

ASTRO
- 099-16 Mucositis (?)

AAPMed
- 3041 NeP
- 3042 LBP
- ISS
- ISE

APS
- 3040 BTP OL Safety
- 3040 BTP OL Safety (QoL)
- ISS
- ISE

ASCO
- 099-15 BTCP OL Safety (efficacy)
- 099-15 BTCP OL Safety (ACTIQ switch/pref)

ON HOLD – Per Taiho (until after 099-11 and -18 are published)
- 099-19 Dose Proport
- 099-20 MD PK
- 099-21 Bioequivalence

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*Pending acceptance

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PK Primary Publications: 099-11

Study	099-11
Title	**Bioavailability and Dose Proportionality of Fentanyl Effervescent Buccal Tablets in Healthy Volunteers**
Summary	▪ Total fentanyl exposure after FEBT is equivalent to a higher dose of fentanyl administered as ACTIQ (FEBT is more potent) ▪ C_{max} is higher and T_{max} is earlier after FEBT than after a higher dose of ACTIQ ▪ Total serum fentanyl is proportional to dose within the range of 270 µg to 1300 µg FEBT
Message Themes	Pharmacokinetics
Author(s)	M Darwish, K Tempero, M Kirby, J Thomson
Target Journal	***Clinical Therapeutics* (IF 2.67, 1-3 months)** *or J Pharmacokin Pharmacodyn* (IF 1.625, 4-6 months)
Timelines	In development. Target submission date Jul 05, est. publish Oct-Nov 05

Stick w/ Clin Ther - higher IF journal, shorter sub to pub time
NOTE: If we follow this time course, we risk being unable to present this data at ASA.

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PK Primary Publications: 099-18

Study	099-18 Dose Proportionality
Title	**Pharmacokinetics and Dose Proportionality of the Investigational Agent Fentanyl Effervescent Buccal Tablets**
Summary	▪ There is dose proportionality across the range of 200-810 μg FEBT
Message Themes	Pharmacokinetics
Author(s)	M Darwish, K Tempero, M Kirby, J Thomson
Target Journal	*CNS Drugs* (IF 3.804, 5-9 months)
Timelines	In development. Target submission date Jul 05, est. publish Apr 06

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PK Primary Publications: 099-19

Study	099-19 Dose Proportionality (Taiho)
Title	**Investigation of the Pharmacokinetics of Fentanyl Effervescent Buccal Tablets in Healthy Japanese Subjects**
Summary	▪ There is dose proportionality across the range of 100-800 μg FEBT
Message Themes	Pharmacokinetics
Author(s)	Study Investigator(s), CIMA/Cephalon internal representatives
Target Journal	*Pharmacotherapy* (IF 2.002, 5-8 months)
Timelines	Development **on hold** until after the 099-11 and 099-18 manuscripts are published – per Taiho

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PK Primary Publications: 099-20

Study	099-20 MD PK (Taiho)
Title	**Pharmacokinetic Profile of Fentanyl Effervescent Buccal Tablets in Healthy Japanese Subjects**
Summary	▪ Multidose PK profile of 200 and 400 μg FEBT in healthy Japanese adults
Message Themes	Pharmacokinetics
Author(s)	Study Investigator(s), CIMA/Cephalon internal representatives
Target Journal	*Clin Drug Invest* (IF .709, 5-8 months)
Timelines	Development **on hold** until after the 099-11 and 099-18 manuscripts are published – per Taiho

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PK Primary Publications: 099-21

Study	099-21 Bioequivalence (Taiho)
Title	**Pharmacokinetics and Bioavailability of Fentanyl Effervescent Buccal Tablets in Healthy Japanese Subjects**
Summary	▪ PK data for 2x200 μg doses of FEBT vs 1x400 μg dose of FEBT ▪ Equivalent AUC, C_{max} and T_{max} ▪ Patients can safely use multiple doses to titrate to an effective dose
Message Themes	Pharmacokinetics/Bioequivalence
Author(s)	Study Investigator(s), CIMA/Cephalon internal representatives
Target Journal	*Pharmacotherapy* (IF 2.002, 5-8 months)
Timelines	Begin development 3Q 06, submit 4Q 06, est. publish 2Q 07

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PK Primary Publications: 1026

Study	1026 Bioequivalence
Title	**Relative Bioavailability of Fentanyl Effervescent Buccal Tablets: Results of a Randomized, Open-label, Crossover Study in Healthy Volunteers**
Summary	▪ PK data for 4x100 μg doses of FEBT vs 1x400 μg dose of FEBT ▪ Equivalent AUC, C_{max} and T_{max} ▪ Patients can safely use multiple doses to titrate to an effective dose
Message Themes	Pharmacokinetics/Bioequivalence
Author(s)	M Darwish, M Kirby, P Robertson, E Hellreigel, J Jiang
Target Journal	*Clinical Pharmacokinetics* (IF 3.899, 5-9 months)
Timelines	In development. Target submission date Oct 05, est. publish Jun 06

NOTE: If we follow this time course, we risk being unable to present this data at ASCO (publication could be right before the congress).

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PK Primary Publications: 1027

Study	1027 Dose Proportionality
Title	**Pharmacokinetic Properties of Fentanyl Effervescent Buccal Tablets: An Open-Label Crossover Study in Healthy Adult Volunteers**
Summary	▪ There is dose proportionality across the range of 100-800 μg FEBT
Message Themes	Pharmacokinetics
Author(s)	M Darwish, M Kirby, P Robertson, W Tracewell, J Jiang
Target Journal	*Pharmacotherapy* (IF 2.002, 5-8 months)
Timelines	In development. Target submission date Sep 05, est. publish May 06

NOTE: If we follow this time course, we risk being unable to present this data at AAPM&R.

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PK Primary Publications: 1028

Study	1028 Absolute Bioavailability
Title	**Comparative bioavailability of the novel Fentanyl Effervescent Buccal Tablets formulation—an open-label crossover study**
Summary	▪ Present the absolute and relative bioavailability of 800 μg FEBT vs 800 μg ACTIQ, IV and PO fentanyl in healthy volunteers ▪ Potency of FEBT vs ACTIQ
Message Themes	Pharmacokinetics
Author(s)	M Darwish, M Kirby, P Robertson, W Tracewell, J Jiang
Target Journal	*J Pain Symptom Management* (IF 1.508, 8-11 months)
Timelines	In development. Target submission date Oct 05, est. publish Sep 06

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PK Primary Publications: 1029

Study	1029 MD PK
Title	**Multiple Dose Pharmacokinetics of Fentanyl Effervescent Buccal Tablets in Healthy Volunteers**
Summary	▪ Present the steady state PK data for 400 μg FEBT ▪ No unexpected drug accumulation
Message Themes	Pharmacokinetics
Author(s)	M Darwish, M Kirby, P Robertson, E Hellreigel, J Jiang
Target Journal	*J Pharmacokin Pharmacodyn* (IF 1.625, 4-6 months)
Timelines	In development. Target submission date Sep 05, est. publish Mar 06

NOTE: If we follow this time course, we risk being unable to present this data at APS.

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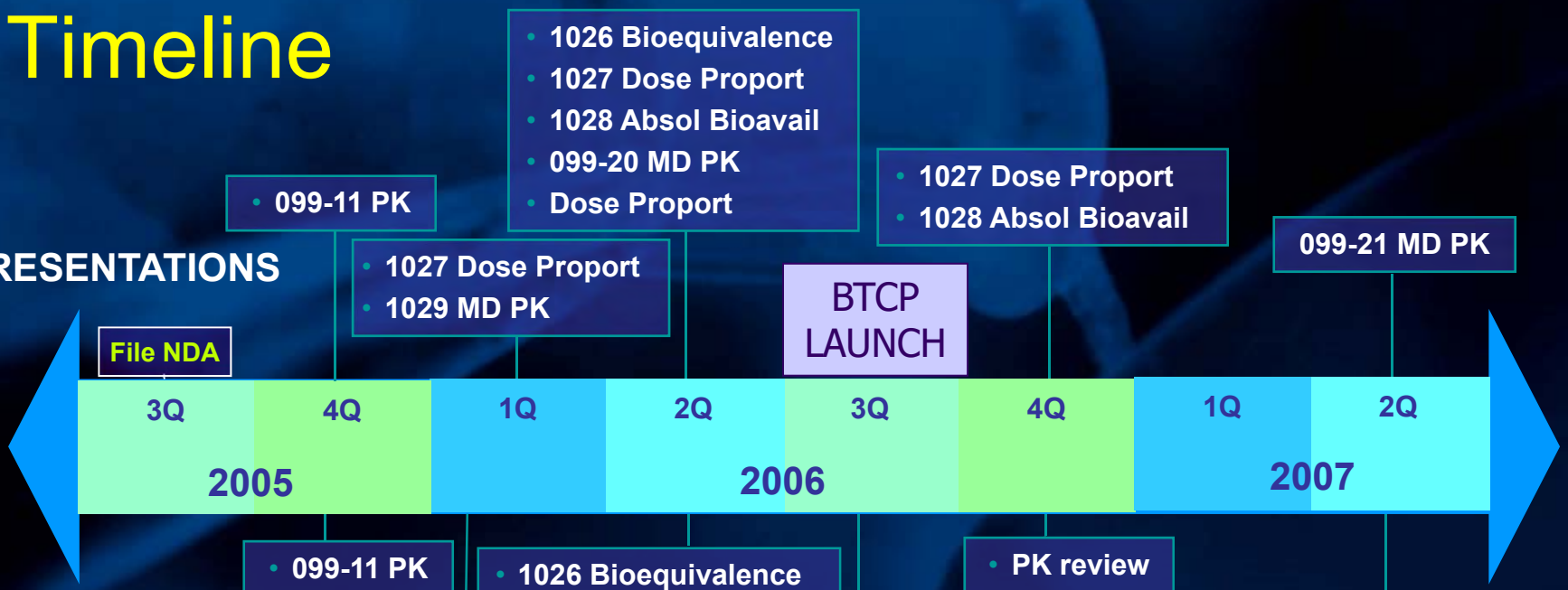
PK Trials Publication/Presentation Timeline



ON HOLD – Per Taiho (until after 099-11 and -18 are published)
- 099-19 Dose Proport
- 099-20 MD PK
- 099-21 Bioequivalence

- 099-18 PK
- 1029 MD PK

Data Availability:

099-11 PK	available	1026 Bioequivalence	available
099-18 PK	available	1027 Dose Proport	available
099-19 PK	on hold	1028 Absol Bioavail	available
099-20 MD PK	2Q 05	1029 MD PK	available
099-21 MD PK	2Q 06		

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Efficacy Primary Publications: 099-14

Study	099-14 Efficacy (pivotal study)
Title	**Randomized Placebo-Controlled Trial of Fentanyl Effervescent Buccal Tablets as Treatment for Breakthrough Pain in Opioid-tolerant Cancer Patients**
Summary	▪ FEBT is effective in managing BTP in opioid-tolerant cancer patients ▪ On average the time between BTP episodes was >6 hrs with FEBT treatment while BTP episodes were more frequent with PBO
Message Themes	Clinical Efficacy
Author(s)	R Portenoy, D Taylor, J Messina, L Tremmel
Target Journal	***Clinical Journal of Pain* (IF 2.662, 5-7 months)** or *J Pain Symptom Management* (IF 1.508, 8-11 months)
Timelines	In development. Target submission date Sep 05, est. publish Apr 06

Stick w/ Clin J Pain for the higher IF journal and shorter sub to pub time

NOTE: If we follow this time course, we would be unable to re-present this data at ONS and 1st presentation at AAPMed could be affected if it was pub'd at the shorter end of the time to pub estimate.

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Efficacy Primary Publications: 099-15

Study	099-15 Safety
Title	**Long-term Safety and Tolerability in Breakthrough Pain Management in Cancer With Fentanyl Effervescent Buccal Tablets**
Summary	▪ Long-term safety of FEBT ▪ After 1 year of treatment with FEBT, xx% of patients continued to achieve good pain control ▪ ACTIQ switching/preference messages
Message Themes	Safety and Efficacy
Author(s)	Study Investigator, Cephalon internal representative(s)
Target Journal	*Journal of Clinical Oncology* (IF 10.864, 4-6 months)
Timelines	Begin development Sep/Oct 05, submit Jan/Feb 06, est. publish Jun/Jul 06

NOTE: If we follow this time course, we risk being unable to present this data at ASCO (publication could be right before the congress).

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Efficacy Primary Publications: 099-16

Study	099-16 Mucositis
Title	**Single-dose Pharmacokinetic Study of Fentanyl Effervescent Buccal Tablets in Cancer Patients With Mucositis**
Summary	▪ Tolerability and PK of 200 μg FEBT in cancer patients with mucositis
Message Themes	Efficacy/Pharmacokinetics
Author(s)	Study Investigator, Cephalon internal representative(s)
Target Journal	*Radiotherapy and Oncology* (IF 2.469, 2-6 months)
Timelines	Begin development 4Q 05, submit 2Q 06, est. publish 4Q 06

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Efficacy Primary Publications: 3039

Study	3039 Onset of action (pivotal study)
Title	**Efficacy and Onset of Action of Fentanyl Effervescent Buccal Tablets in a Double-blind, Randomized Trial of Breakthrough Pain in Cancer**
Summary	▪ FEBT is effective in managing BTP in opioid-tolerant cancer patients ▪ On average the time between BTP episodes was >6 hrs with FEBT treatment while BTP episodes were more frequent with PBO ▪ Time of analgesic onset with FEBT is <15 minutes ▪ FEBT is superior to PBO in controlling pain through 2 hours ▪ ACTIQ switching/preference messages
Message Themes	Clinical Efficacy
Author(s)	J Farrar, T Segal, Cephalon internal representative(s)
Target Journal	***Anesthesia & Analgesia* (IF 2.21, 8-9 months)** or *J Pain* (IF 3.2, 5-11 months)
Timelines	Begin development Oct 05, submit Jan 05, est. publish Sep 06

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Potential ISS/ISE Data for Presentations and Articles

- ISS (combines safety data from 099-14, 099-15 and 3039 cancer BTP studies)
  - Data tables may be available July 2006
  - Abstract to AAPMed or APS for 2007 presentation?
- ISE (combines efficacy data from 3014 and 3039 cancer BTP efficacy studies)
  - Abstract to AAPMed or APS for 2007 presentation?
  - Primary manuscript?

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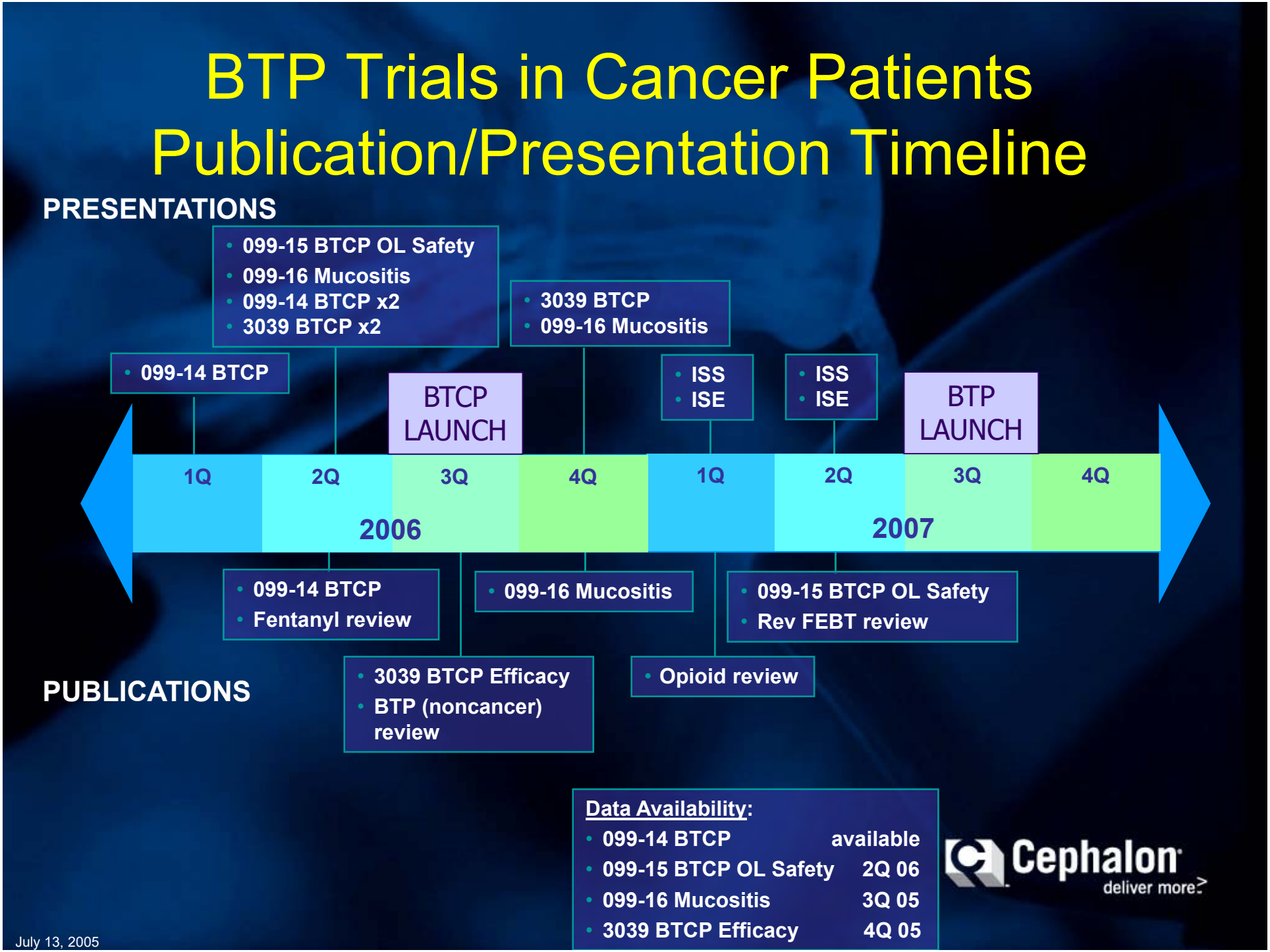
BTP Trials in Cancer Patients Publication/Presentation Timeline



Data Availability:

099-14 BTCP	available
099-15 BTCP OL Safety	2Q 06
099-16 Mucositis	3Q 05
3039 BTCP Efficacy	4Q 05

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Efficacy Primary Publications: 3040

Study	3040 BTP OL Safety
Title	**Fentanyl Effervescent Buccal Tablets in the Long-term Management of Non-cancer BTP**
Summary	▪ Long-term (up to 1 year) safety of FEBT ▪ After 1 year of treatment with FEBT, xx% of patients continued to achieve good pain control
Message Themes	Safety
Author(s)	Study Investigator, Cephalon internal representative(s)
Target Journal	*J Pain Symptom Management* (IF 1.508, 8-11 months)
Timelines	Begin development 3Q 06, submit 1Q 06, est. publish 4Q 07

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Efficacy Primary Publications: 3041

Study	3041 NeP Efficacy/Safety (pivotal study)
Title	**Fentanyl Effervescent Buccal Tablets Alleviates BTP in Patients with Chronic Neuropathic Pain**
Summary	▪ FEBT is effective in managing BTP in opioid-tolerant chronic non-cancer pain patients ▪ On average the time between BTP episodes was >6 hrs with FEBT treatment while BTP episodes were more frequent with PBO ▪ Time of onset of analgesia with FEBT is <15 minutes ▪ FEBT is superior to PBO in controlling pain through 2 hours
Message Themes	Efficacy/Safety
Author(s)	Study Investigator, Cephalon internal representative(s)
Target Journal	***Pain* (IF 4.829, 5-10 months)** or *Neurology* (IF 5.678, 3-8 months)
Timelines	Begin development Apr 06, submit Aug 06, est. publish Jun 07

Far more common to see NeP studies in pain journals, Neurol was the only journal to recently pub NeP trials, thus chance of acceptance may be better at Pain w/ no major time diff

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Efficacy Primary Publications: 3042

Study	3042 LBP Efficacy/Safety
Title	**A Randomized Controlled Trial of Fentanyl Effervescent Buccal Tablets in Patients with Chronic Low Back Pain**
Summary	▪ FEBT is effective in managing BTP in opioid-tolerant chronic non-cancer pain patients ▪ On average the time between BTP episodes was >6 hrs with FEBT treatment while BTP episodes were more frequent with PBO ▪ Time of onset of analgesia with FEBT is <15 minutes ▪ FEBT is superior to PBO in controlling pain through 2 hours
Message Themes	Efficacy/Safety
Author(s)	Study Investigator, Cephalon internal representative(s)
Target Journal	***Anesthesia & Analgesia* (IF 2.21, 8-9 months)** or *Clin Ther* (IF 2.67, 1-3 months)
Timelines	Begin development Jun 06, submit Oct 06, est. publish Jul 07

Anesth & Analg had more LBP articles in the last 2 yrs, but if timing is an issue, could potentially be less time to pub w/ Clin Ther

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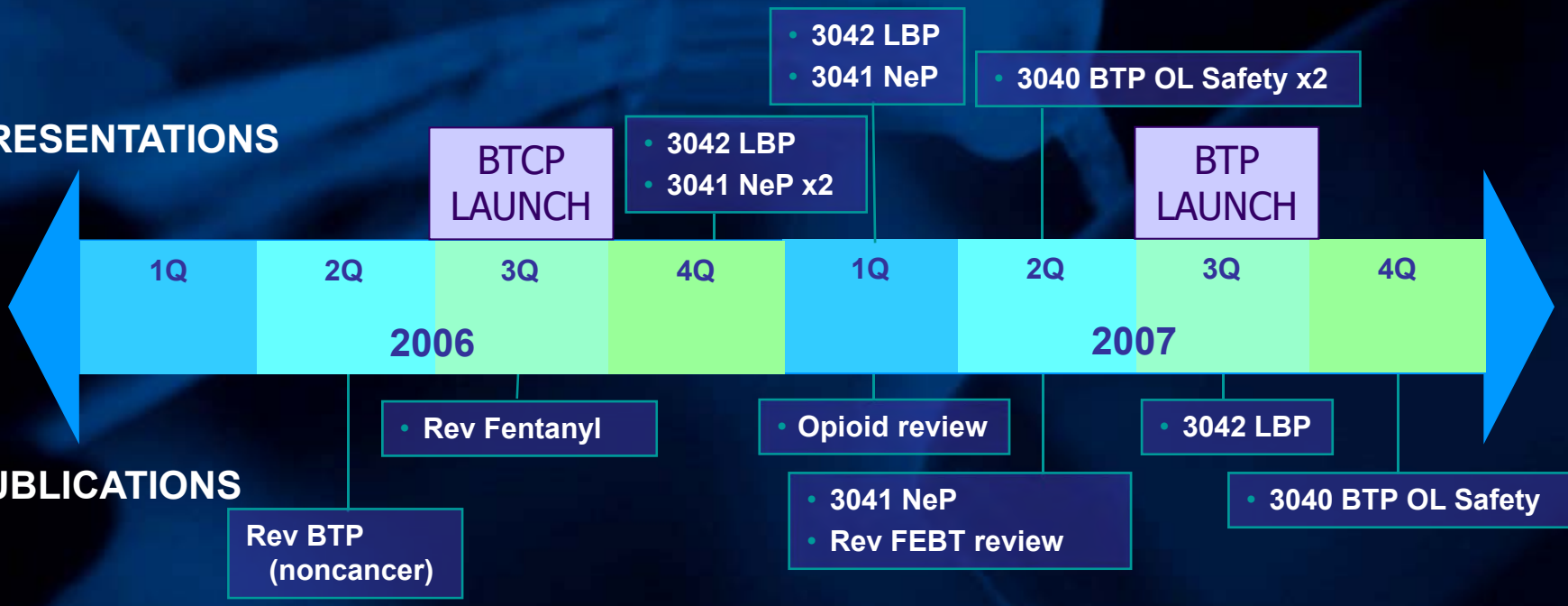
Noncancer BTP Trials Publication/ Presentation Timeline



Data Availability:

• 3041 LBP	1Q 06
• 3042 NeP	1Q 06
• 3040 BTP OL Safety	3Q 06

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Review Manuscript: Fentanyl

Title	**Choice of fentanyl formulations: strategies to achieve optimal pain management for the patient**
Summary	▪ Match type of pain to route of fentanyl administration to highlight importance of considering time to onset and duration of pain in choosing appropriate therapy - Review strengths/weaknesses/appropriate uses of intravenous, oral, transdermal patch, OTFC, FEBT and intranasal routes of administration - Scene-setting for trials/use of FEBT – faster T_{max}, higher C_{max} and AUC than OTFC should translate to improved efficacy in BTP treatment
Message Themes	Disease awareness, Efficacy, Safety & tolerability, MOA
Author(s)	Rich Payne
Audience	Pharmacists, PCPs, Internists
Target Journal	*Clinical Pharmacokinetics* (IF 3.899, 5-9 months)
Timelines	Begin development Aug 05, submit Nov 05, est. publish Aug 06

Publish after PK study publications and before clinical efficacy study publications

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July 13, 2005

Review Ms: BTP

Title	**Pharmacologic management of chronic noncancer BTP**
Summary	▪ Impact and consequences of poorly managed BTP in noncancer pain conditions (include Portenoy/SAGEMed new data) ▪ Challenges in BTP management ▪ Review appropriate use of opioids in treatment of moderate to severe noncancer pain (guidelines, etc) - Highlight the relative lack of clinical data for opioids in many of these painful conditions (rather treatment plans are extrapolated based on results from cancer BTP studies) - Scene-set for FEBT, rapid-onset opioids as ideal for BTP - Discuss benefits/drawbacks of available treatments ▪ Discuss issues of safety/tolerance/addiction
Message Themes	Disease awareness
Author(s)	Russ Portenoy
Audience	Clinicians in a variety of research, academic and clinical practice settings
Target Journal	*Clinical Therapeutics* (IF 2.67, 1-3 months)
Timelines	Begin development Nov 05, submit Mar 06, est. publish Jun 06

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Review Ms: PK Review

Title	**Evaluating the pharmacokinetics of FEBT**
Summary	▪ A secondary publication gathering together all available FEBT PK data as a review article. ▪ Potential venue to present dose proportionality analysis across the full dose range tested. ▪ Would go though additional internal scrutiny to permit its use as a field force handout.
Message Themes	PK profile, MOA
Author(s)	Dennis Turk, Brian Ginsberg
Audience	Pain specialists
Target Journal	*Clin Pharmacokinet* (IF 3.899, 5-9 months)
Timelines	Begin development Sept 05, submit Feb 06, est. publish Nov 06

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Review Ms: FEBT Review

Title	**FEBT: A New Treatment for BTP**
Summary	▪ A secondary publication gathering together all available FEBT clinical and PK data as a review article. ▪ Would go though additional internal scrutiny to permit its use as a field force handout.
Message Themes	FEBT efficacy, safety, tolerability, good PK
Author(s)	Key opinion leader (TBD)
Audience	Oncologists, neurologists, anesthesiologists, pain specialists
Target Journal	*Journal of Pain* (IF 3.2, 5-11 months) or an Adis journal
Timelines	Begin development Jan 06, submit May 06, est. publish Apr 07

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Review Manuscript: Opiates Review

Title	**Abuse and appropriate use of prescription opiates**
Summary	▪ Educate readers on why these drugs are controlled, what that means in terms of prescribing them, how to recognize misuse/abuse by patients and what to do about it. ▪ Discuss problems w/ prescribing opioids (clinical practice) or filling opioid prescriptions (pharmacy) ▪ Government classifications and restrictions ▪ In response to National Center on Addiction and Substance Abuse findings that few MDs or pharmacists have had much training in prescribing these drugs or recognizing abuse/diversion.
Message Themes	Safe, effective pain management
Author(s)	Key opinion leader (TBD)
Audience	General practitioners, pharmacists
Target Journal	*Am J Health-Syst Pharmacy* (IF 1.44, 4-5 months) or *Postgrad Med* (IF 0.901, 10-11 months)
Timelines	Begin development Oct 05, submit Mar 06, est. publish Feb 07

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Potential Topics for Scene-Setting/ Review Articles: Highest Priority

- Definition of BTP and pain types in general
  - Distill types of pain into separate categories
  - Literature review with a big name KOL to champion it
- Evolution of pharmacotherapeutic management of pain
  - Review the last decade of pain management learnings
  - Growing diagnostic and treatment sophistication
  - Define rapid-onset opioids (ROOs)
  - Comprehensive review of short-acting opioids (SAOs), long-acting opioids (LAOs), and ROOs
- Effective multidisciplinary approach to managing pain *
  - Discuss problems w/ prescribing opioids (clinical practice) or filling opioid prescriptions (pharmacy)
  - Government classifications and restrictions
  - Managed care
  - Others

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* Consider inclusion of starred ideas in a pain journal supplement

Potential Topics for Scene-Setting/ Review Articles: Highest Priority

- Outcomes/quality of life review of inadequately treated pain
- Pain assessment literature *
  - Currently lacking for BTP and need for a validated BTP assessment tool
  - Aside from the new BTP guidelines, most pain management guidelines do not discuss BTP assessment and management
- Managed care/health economics review *
- Fentanyl review article

* Consider inclusion of starred ideas in a pain journal supplement

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Potential Topics for Scene-Setting/ Review Articles: Medium Priority

- Epidemiology of BTP
  - Perform Medline search on BTP patient populations using BTP guidelines Part 1 for specifics on search terms
  - Cancer, low back pain, fibromyalgia, post-surgery, etc
  - Survey/review of the rates of chronic pain patients on LAOs who have BTP
- Systematic review of all PK and PD data associated with both OTFC and FEBT
  - Possible assignment to Adis to write/publish in one of their journals
  - Arterial vs venous sampling/correlates
- Chemical coping – evidence or perception?
  - Consider Steve Pasik as lead author

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Potential Topics for Scene-Setting/ Review Articles: Low Priority

- Opioid rotation – pros and cons
- Opioid use in primary care (and how to optimize use in primary care settings
- Hormonal and cardiovascular effects of long-term opioid use
  - FEBT similar to PCA?

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Potential Topics for Journal Supplement

- Starred concepts from previous slides:
  - BTP assessment/lack of validated tools
  - Managed care/HE review
  - Multidisciplinary approach to pain care

PLUS

- Targeted article for pharmacists or nurses
- Pain is not a symptom – it's a syndrome
- What every opioid prescriber should know

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Overview: Estimated Publication Dates

- 099-11 PK
- 099-18 PK
- 1029 MD PK
- 099-14 BTCP Efficacy
- 1026 Bioequivalence
- 1027 Dose Proportionality
- 099-19 PK
- BTP (noncancer) review
- Opioid review
- 099-16 Mucositis
- PK review
- 3039 Onset of Action
- 1028 Absolute Bioavail
- 099-20 MD PK
- Fentanyl review
- 3042 LBP
- 099-15 BTCP OL Safety
- 3041 NeP
- 3040 BTP OL Safety
- 099-21 MD PK
- FEBT review

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Appendix

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Independent Studies Presentations 2005

Congress	Studies	Abstract Status	Location	Meeting Date
AAPMed	▪ Prev. of BTP in NeP (Simon) ▪ Prev. of BTP in back pain (Bennett)	Presented	Palm Springs	Feb 2005
APS	▪ OTFC in NeP (Farrar) ▪ Pain intol. In NC-BTP (Bruns) ▪ Prev. of NC-BTP (Portenoy)	Presented	Boston	Mar 2005
AAPM&R	▪ 2 Sagemed abstracts	?	Philadelphia	Oct 2005
IASP	▪ BTP mgmt in non-CA pain (Rauck) ▪ BTP mgmt in chronic low back pain (Bennett)	Accepted Accepted	Sydney	Aug 2005

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Abstracts Presented 2005: AAPMed

- American Association of Pain Medicine (AAPMed) Annual Meeting, February 23-27, 2005
  - Abstracts published in March issue of Journal of Pain
  - Prevalence and Characteristics of Breakthrough Pain in Noncancer Patients with Chronic Neuropathic Pain. S Simon, DS Bennett, R Rauck, D Taylor, S Shoemaker
  - Prevalence and Characteristics of Breakthrough Pain in Noncancer Patients with Chronic Back Pain. DS Bennett, S Simon, RL Rauck, D Taylor, S Shoemaker

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Abstracts Presented 2005: APS

- American Pain Society (APS) Annual Meeting, March 30-April 2, 2005
  - Abstracts to be published in the April supplement of Journal of Pain
  - Oral Transmucosal Fentanyl Citrate: Efficacy in Neuropathic Pain Patients. J Farrar, C Thompson
  - Degree of pain intolerance and adverse outcomes in chronic noncancer pain patients. D Bruns, J Disorbio, D Bennett, S Simon, S Shoemaker, R Portenoy
  - Prevalence and characteristics of breakthrough pain in patients with chronic noncancer pain. R Portenoy, D Bennett, S Simon, R Rauck, D Taylor, S Shoemaker

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